Vedolizumab (ENTYVIO) for Intravenous Injection

Criteria for Use

December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria *If ANY item below applies, then the patient should NOT receive vedolizumab.*

- ☐ Known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients
- ☐ Active tuberculosis
- ☐ Uncontrolled, active, severe infection including evidence of *C. difficile*
- ☐ Congenital or acquired immunodeficiency
- ☐ Known or suspected progressive multifocal leukoencephalopathy (PML)
- ☐ Concomitant treatment with natalizumab (potential increased risk of PML)
- ☐ Concomitant treatment with tumor necrosis factor inhibitors / TNFIs (not studied)
- ☐ Primary nonresponse to natalizumab (vedolizumab has a similar mechanism)

Inclusion Criteria *All of the following should be fulfilled in order to meet criteria.*

☐ **A.** Receiving VA care or consultation from a gastroenterologist or other expert in the treatment of inflammatory bowel disease and the initial prescription is written by this provider

AND

☐ **B.** Patient is up to date with all immunizations according to current CDC immunization guidelines.
Patients who need vedolizumab before vaccination is possible, and other exceptions to criterion B, should be considered case by case.

AND

☐ **C.** Is an adult outpatient with **EITHER** of the following conditions:

___ Moderately to severely active **ulcerative colitis (UC)**

___ Moderately to severely active inflammatory **Crohn's disease (CD)**

AND D or E applies:

☐ **D.** The patient has one of the following conditions that precludes the use of TNFI therapy:

___ History of prior extraintestinal malignancy less than 5 years ago, excluding nonmelanoma skin cancer.

___ Current undrainable gastrointestinal abscess.

___ Solid organ transplant.

OR

☐ **E.** The patient has had adequate therapeutic trials of **ONE of the following treatments**, unless the patient has a contraindication, risk factor for serious adverse event*, or intolerance to the agent(s)**:**

(Criterion 1 is an option with or without therapeutic drug monitoring.)

___ 1. **A TNFI and an antimetabolite immunomodulator**, separately or in combination.

OR

___ 2. **An initial and second TNFI**, if therapeutic drug monitoring after secondary nonresponse to TNFI therapy indicates high titers of anti-TNFI antibodies.

OR

___ 3. **A TNFI,** when either of the following apply:

- o Induction therapy with an agent from a different biologic class is needed to treat an inadequate response (with confirmed active inflammation / persistent disease) following TNFI induction therapy (i.e., primary nonresponse) and therapeutic drug monitoring shows therapeutic or high trough TNFI serum concentrations.
- o The patient lost response (i.e., secondary nonresponse not due to adverse reaction) to the initial TNFI in association with therapeutic or high trough TNFI serum concentrations.

* Examples of **risk factors for serious adverse effects** include cardiac failure, hematologic cytopenias, demyelinating disease, concurrent malignancy (class adverse reactions for TNFIs) or reactivation of hepatitis B infection (for antimetabolite drugs and TNFIs) and deficiency in thiopurine methyltransferase (TPMT) activity (for thiopurine antimetabolite drugs).

See Definitions > Primary nonresponse and Secondary nonresponse to TNFIs, Alternative Pharmacologic Therapies for Moderate to Severe, Active UC or CD, and Relative Drug Acquisition Costs.

Dosage and Administration

Refer to Product Information.

The product must be reconstituted and diluted according to the instructions provided in the product information.

Dosage in Adults with Ulcerative Colitis or Crohn's Disease: 300 mg administered by intravenous infusion over 30 minutes at 0, 2 and 6 weeks and then every 8 weeks thereafter.

Vedolizumab must be administered by a health care professional as an **intravenous infusion over 30 minutes**. Do not administer by intravenous push or bolus.

Renal or Hepatic Impairment: No pharmacokinetic studies. No recommendations on dosage modification.

Geriatric Use: No recommendations on dosage modification.

Storage: If necessary, the infusion solution may be stored for up to four hours at 2° to 8°C (36º to 46ºF). Do not freeze. Discard any unused portion of the infusion solution**.**

Monitoring

Effectiveness of Therapy

- Generally, the goals of therapy are symptomatic response and glucocorticoid-free symptomatic remission.
- **Tools** that are considered practical for monitoring patient response to therapy include the Mayo score for assessing UC activity and the Harvey-Bradshaw Index (HBI), a symptom-based scoring system for assessing Crohn's disease activity.
- **Laboratory monitoring:** In UC, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are nonspecific inflammatory markers that have been shown to correlate with disease activity; however, not all patients with active disease mount increases in serum markers of inflammation such as ESR and CRP. Fecal calprotectin and lactoferrin are also used to monitor UC disease activity. In CD, C-reactive protein (CRP) and fecal calprotectin and lactoferrin are biomarkers that may indicate the presence of active inflammation.

  Therapeutic Drug Monitoring (TDM) in Secondary Nonresponders with Evidence of Active Inflammation: Assuming valid and reliable TNFI and antibody assays are used, if antibodies are not detected and TNFI trough levels are low, the dosing regimen of the initial TNFI may be empirically optimized by increasing the dose or shortening the dosing interval. If antibodies are detected and TNFI trough levels are adequate (or if TDM is not available), the treatment approach (e.g., switching to another TNFI or vedolizumab) should be based on the physician's discretion. However, the relative benefits, risks and costs of therapy should be considered; the second TNFI or vedolizumab in TNFI secondary nonresponders seems to be less likely than the first TNFI to achieve a clinical response or remission. Vedolizumab is more costly than TNFIs (see Relative Drug Acquisition Costs). The TNFIs used for UC and CD are comparable in efficacy and safety; therefore, the less costly TNFI agents are preferable. When a patient develops intolerance to an initial TNFI, a trial of another TNFI or switching to an agent in another class, such as vedolizumab, may be appropriate, depending partly on the nature of the adverse effect. Also see *Issues for Consideration > Definitions > Secondary Nonresponse*.

Safety

- Monitor patients during and after vedolizumab infusions for hypersensitivity reactions including anaphylaxis. Appropriate monitoring and medical support measures should be available for immediate use. If anaphylaxis or other serious allergic reactions occur, immediately discontinue administration of vedolizumab and administer treatment such as epinephrine and antihistamines.
- Patients receiving vedolizumab are at increased risk for infections. Serious infections have included anal abscess, sepsis, tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis. The most common infections involved the upper respiratory tract and nasal mucosa. Vedolizumab is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding vedolizumab if a severe infection develops during treatment.
- Consider screening for tuberculosis (TB) according to local practice.
- New or worsening neurological signs or symptoms. If PML is suspected, withhold dosing of vedolizumab. If confirmed, discontinue vedolizumab.
- Liver Injury. There is a potential risk of drug-induced liver injury. Discontinue vedolizumab in patients with jaundice or symptoms consistent with hepatitis or significant liver injury. In premarketing clinical trials, "marked abnormalities" were defined as ALT or AST > 3 times the upper limit of normal (ULN) or bilirubin > 2 times ULN.
- Hepatitis B Reactivation. Although vedolizumab has not been associated with reactivation of hepatitis B, there is a possibility that vedolizumab may cause reactivation of hepatitis B. Clinical trials excluded patients with chronic hepatitis B (or C) infection. Routine screening for markers of HBV infection before starting therapy is not a recommendation in the product information, but such screening is prudent. Monitor HBsAg– or anti-HBc–positive patients for reactivation and treat patients with antiviral therapy if HBV DNA or HBsAg is detected.

Issues for Consideration

Definitions

- **Glucocorticoid refractoriness** may be defined as no meaningful clinical response within 2 weeks of starting oral induction therapy using the equivalent of prednisone 30 to 60 mg/day for 2 weeks (then tapering over the next 2 weeks) for oral therapy or 1 to 1.5 weeks for intravenous therapy or using budesonide extended-release tablets (UCERIS or equivalent product) 9 mg/day for 4 weeks.
- **Glucocorticoid dependency** may be defined as two unsuccessful attempts on separate occasions to taper, without disease recurrence, to less than 10 mg/day of prednisone or equivalent within 3 months of starting glucocorticoids OR relapse occurring within 3 months of stopping glucocorticoids.
- **Primary nonresponse** refers to a lack of response to TNFI therapy. Possible causes for a failure to respond include inflammation that is promulgated mainly by non-TNF factors (i.e., mechanistic tolerance or mechanistic escape). For primary nonresponders, switching to an agent with a different, non-TNF mechanism would be rational. Ideally, other possible causes for nonresponse should be ruled out before labeling a patient a primary nonresponder. Lack of response may be due to noninflammatory conditions (e.g., lactose intolerance, irritable bowel syndrome), disease complications (such as fibrostenotic stricture, abscess or irreversible structural lesion) or symptoms unrelated to inflammatory bowel disease (IBD) (such as concurrent *C. difficile* infection.
- **Secondary nonresponse** refers to situations in which patients initially respond to TNFI therapy then lose response to their initial TNFI. Assuming noninflammatory conditions, disease-related complications and non-IBD conditions have been ruled out as possible explanations for loss of response, serum TNFI trough levels and TNFI antibody titers can help determine the cause of loss of response and guide management. Human anti-chimeric antibody (HACA) formation to infliximab occurs more frequently than human anti-human antibody (HAHA) formation to the fully human or humanized TNFIs (e.g., adalimumab, certolizumab, golimumab). Concurrent immunosuppressive agents may reduce antibody formation. The presence of neutralizing antibodies have been associated with reduction in duration of response to treatment, decreased drug levels or accelerated drug clearance.
- **Symptomatic response.** The Toronto Consensus guidelines for medical management of nonhospitalized UC defines symptomatic response as "meaningful improvement in symptoms as judged by both the patient and provider in the absence of remission; symptomatic response should not be considered a desirable final outcome but is useful to assess early response to treatment."[1]
  Symptomatic remission. For UC, the Toronto Consensus guidelines define symptomatic remission as normal stool frequency (≤ 3 / day) and no blood in the stool.[1] For CD, according to the American College of Gastroenterologists, an "individual is in symptomatic remission (usually corresponding to a Crohn's Disease Activity Index (CDAI) < 150) when that patient is asymptomatic or without any symptomatic inflammatory sequelae. Individuals included in this category may have responded to medical therapy or surgical therapy (such as ileocolonic resection) and have no residual active disease. Individuals who require the use of conventional corticosteroids to achieve clinical well-being are said to be "steroid dependent" and are not considered to be in remission."

FDA Indications. Vedolizumab is an integrin receptor antagonist indicated for:

- **Adult Ulcerative Colitis (UC)**

  Inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving glucocorticoid-free remission in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a TNFI or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on glucocorticoids.

- **Adult Crohn's Disease (CD)**

  Achieving clinical response, achieving clinical remission, and achieving glucocorticoid-free remission in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNFI or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on glucocorticoids.

Relatively Gut-selective Immune Effects and Potential Advantages

- **Off-target Adverse Reactions.** Vedolizumab does not seem to be entirely "gut selective." According to the FDA Medical Review of vedolizumab, there are data suggesting that MAdCAM1 receptors for alpha-4-beta-7 integrin exist outside the gastrointestinal tract.[2] Hematologic laboratory data and respiratory and dermal adverse reactions and perhaps bone marrow and peripheral nervous system adverse reactions seemed to show that vedolizumab has off-target, extraintestinal effects. Those adverse reactions included upper respiratory tract infection, paresthesias / dysesthesias suggestive of peripheral neuropathy, epidermal and dermal conditions / apocrine and eccrine disorders including folliculitis, and an inconsistently observed increase in peripheral neutrophil and myelocyte counts.
- Like natalizumab, vedolizumab **lacks warnings and precautions for invasive fungal infections, hepatitis B reactivation, cardiac failure, hematologic cytopenias, lupus-like syndrome, demyelinating disease and increased risk of malignancies** that have been associated with TNFIs. However, there is less long-term experience with vedolizumab than TNFIs.
- **Serious and Opportunistic Infections.** Serious infections that have been associated with vedolizumab therapy in UC and CD clinical trials include anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis. Serious infections occurred more frequently in patients with CD than in those with UC. Anal abscesses were the most common serious adverse reaction in study patients with CD. There have been no reports of opportunistic infections that commonly occur in immunocompromised patients such as progressive multifocal leukoencephalopathy (PML), systemic candidiasis, disseminated herpes zoster, cytomegalovirus infections outside the gastrointestinal tract, and pneumocystis pneumonia.
- **Live and Oral or Injectable Vaccines.** See **Vaccines**.

Potential Therapeutic Limitations

- **Delayed Onset of Efficacy in CD.** Vedolizumab failed to meet statistical requirements to obtain FDA indications for *induction* of remission and *maintenance* of remission in patients with relatively refractory CD. The induction regimen (300 mg at Weeks 0 and 2) showed no statistically significant benefit in terms of remission rates at Week 6. Post hoc exploratory analyses showed there was significant treatment benefit in achieving remission at Week 10 (after 3 doses: two induction doses at Weeks 0 and 2 plus one maintenance dose at Week 6). Vedolizumab also showed benefit in terms of remission rates at Week 52. An important clinical implication of these findings is that vedolizumab, because it is slow acting, may not be appropriate for patients who require rapid symptom control.
- **Insufficient Evidence of Efficacy for Fistulizing CD.** One of the two major clinical trials provided data on closure of draining fistulae. With vedolizumab dosing every 8 weeks, 46.7% of 17 patients experienced fistula closure compared with 11.1% of 18 placebo-treated patients.[2] The small number of patients prevents drawing conclusions about the efficacy of vedolizumab in patients with fistulizing CD.
- **Lack of Evidence of Efficacy for Extraintestinal Manifestations.** The efficacy of vedolizumab in treating extraintestinal manifestations of UC and CD has not been specifically evaluated.
- **Lack of Evidence of Efficacy for Management of Postsurgical CD.** Vedolizumab has not been evaluated for treatment or prevention of disease recurrence following surgery for CD; however, about 43% of patients in the induction and maintenance clinical trials had a history of prior surgery for CD.
- **Anti-vedolizumab Antibodies.** During 52 weeks of continuous treatment in clinical trials, anti-vedolizumab antibody was detected in 56 (4%) of 1434 of vedolizumab treated patients at any time.[3] Anti-vedolizumab antibody was persistently detected (at $\geq$ 2 study visits) in 9 of the 56 patients and neutralizing antibodies to vedolizumab were detected in 33 of the 56 patients. Of the 9 subjects with persistently positive anti-vedolizumab antibody, 6 had undetectable and 2 had reduced vedolizumab concentrations. None of the 9 subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52.

Progressive Multifocal Leukoencephalopathy (PML)

- Although no cases of PML were observed in clinical trials, a risk of PML cannot be ruled out. No claims about comparative safety relative to other integrin receptor antagonists can be made with the currently available evidence.
- Monitor patients for any new or worsening neurological signs or symptoms, such as progressive weakness on one side of the body, clumsiness of limbs, visual disturbance, confusion and changes in thinking, memory, orientation and personality. PML usually leads to death or severe disability over weeks or months.

- If PML is suspected, withhold doses of vedolizumab and refer patient to a neurologist. If PML is confirmed, discontinue vedolizumab therapy permanently.

Vaccines

- Before initiating vedolizumab therapy, all patients should be brought up to date with all immunizations according to current CDC immunization guidelines.
- Patients receiving vedolizumab therapy may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks.

Specific Populations

- **Pregnancy Category B.** Use only if the benefits to the mother outweigh the risk to the unborn child. Adverse pregnancy effects from vedolizumab would likely be greater during the second and third trimesters of pregnancy, when greater amounts of monoclonal antibodies are transported across the placenta. Information about the ENTYVIO Pregnancy Exposure Registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).
- **Nursing Mothers**: Use caution.
- **Geriatric Use.** Insufficient data to determine whether there is an age-related effect on treatment response.

Alternative Pharmacologic Therapies for Moderate to Severe, Active UC or CD

- The main treatment alternatives to vedolizumab in inflammatory bowel disease (IBD) are shown in Table 1.

Table 1. Adequate Trials of Treatments for Inducing and/or Maintaining Remission

IBD Type	Antimetabolite Immunomodulators (AMIMs)†	TNFIs
Ulcerative Colitis	○ Azathioprine at a minimum dose of 1.5 mg/kg once daily for at least 12 weeks ○ Mercaptopurine at a minimum dose of 0.75 mg/kg once daily for at least 12 weeks ○ *NB: I.m. or s.c. methotrexate does not have established efficacy, and orally administered methotrexate has been shown to be ineffective for induction and maintenance therapy.*	Note: Use standard recommended and evidence-based doses. Based on prescribing information and time period of induction doses, the adequacy of response should be assessed after the time points shown, following induction regimens. For TNFIs, assessment for primary nonresponse at 12–14 weeks has also been suggested.[4] ○ Adalimumab – 8 weeks (Day 57) ○ Golimumab – 6 weeks ○ Infliximab – 14 weeks
Crohn's Disease	○ Azathioprine at a minimum dose of 1.5 mg/kg once daily for at least 12 weeks ○ Mercaptopurine at a minimum dose of 0.75 mg/kg once daily for at least 12 weeks ○ Methotrexate 25 mg i.m. or s.c. once weekly for at least 16 weeks (*NB: In CD, the efficacy of orally administered methotrexate has not been established for induction or maintenance therapy.*)	See note under ulcerative colitis. ○ Adalimumab – 4.1 weeks (Day 29) ○ Certolizumab – 8 weeks ○ Infliximab – 14 weeks ○ Natalizumab – 12 weeks
********Discontinue biologics before initiating vedolizumab********		
† *Notable risk factors for serious adverse events to immunomodulators are **renal failure** and **age > 65 years** (because of decreased immune function / immunosenescence).*		

Relative Drug Acquisition Costs

- When selecting therapy, consider the relative drug acquisition cost of vedolizumab to TNFIs and natalizumab. As of October 2015, certolizumab had the lowest yearly VA drug acquisition price for UC and CD. *Check current cost references for up-to-date drug costs.*
- Table 2 shows the yearly maintenance dose cost ratios for UC and CD relative to certolizumab. For simplicity, the values do not include the costs of induction doses.
- These ratios show that vedolizumab is 5.3 times more costly than certolizumab and 2.5 times more than adalimumab.

Table 2. Relative Costs of Biologics for UC and CD

Biologic Agent	Relative Cost Ratio
Certolizumab	1.0
Adalimumab	2.1
Infliximab	3.0
Vedolizumab	**5.3**
Golimumab	6.8
Natalizumab	8.1

Based on VA drug acquisition costs as of Oct 2015

Renewal Criteria

- Documented benefit by Week 14 of treatment (i.e., by the Week 14 clinic visit following 3 doses at Weeks 0, 2 and 6).
- Discontinue therapy in patients who show no therapeutic benefit by Week 14.

Prepared: December 2015
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REFERENCES

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2 Center for Drug Evaluation and Research. Application Number: 125476Orig1s000. Medical Review(s) of Vedolizumab (ENTYVIO). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125476Orig1s000MedR.pdf

3 ENTYVIO (vedolizumab) Prescribing Information (online). Deerfield, IL: Takeda Pharmaceuticals America, Inc. May 2014.

4 Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimizing response to anti-TNF therapy in Crohn's disease - algorithm for practical management. Aliment Pharmacol Ther. 2015 Oct 30. doi: 10.1111/apt.13445. [Epub ahead of print]